Remarks

The Applicants have amended Claim 1 to remove the phrase "functionally equivalent derivative." Further, the Applicants have amended Claim 22 and 28, to note that it is the cells according to Claim 21, and 27, respectively, that are used to screen substances which modulate ASIC channels. No new matter has been added.

Claim Rejections Under §112, Second Paragraph

Claims 1, 11-13, 15, 17-23, and 26-29 have been rejected under 35 U.S.C. §112, second paragraph. The Applicants respectfully submit that as a result of the amendments to Claims 1, 22 and 28, the rejection is now obviated.

In particular, the Applicants have removed the phrase "functionally equivalent derivative" in Claim 1, and have amended Claims 22 and 28 to point out which cells are contacted with a substance capable of modulating neuronal cationic ASIC channels. Further, the Applicants have corrected minor informalities in Claims 22 and 28.

The Applicants respectfully submit that a study of the Applicants' Specification shows that the measured change in electrophysiological current, upon application of a substance, is clearly due to the modulation of the Applicants' ASIC channel containing the cells according to Claim 21 and 27. In particular, the Applicants respectfully submit that the method disclosed in Claims 22 and 28 describes cells expressing the ASIC channel, wherein the electrophysiological current of the ASIC channels in these cells is measured before and after the substance to be tested has been added to the culture medium. (page 15, line 24 to page 17, line 5 of Applicants' Specification). Hence, the Applicants use a negative control to establish a baseline measure. The Applicants respectfully submit that only one population of cells is contacted with the test

substance, and these cells over-express the ASIC channel. The results demonstrate that cells over-expressing ASIC channel exhibit a measurable change in the electrophysiological current and, as a result, ASIC is the core channel exhibiting electrophysiological current change when contacted with a substance, such as amiloride. In view of the foregoing, the Applicants respectfully request withdrawal of the rejection of independent Claims 1, 22, and 28 and dependent Claims 11-13, 15, 17-21, 23, 26-27 and 29.

Claim Rejections Under 35 U.S.C §101

Claims 1, 11, 12-13, 15, 17, 18- 23, and 26- 29 have been rejected under 35 U.S.C. §101. The Applicants respectfully submit that the pending claims clearly establish a specific and substantial utility.

The Applicants respectfully submit that in light of the amendment to the claims to refer to specific ASIC channels including rat ASIC1a (SEQ ID NO: 2), human ASIC1 (SEQ ID NO: 4), and rat ASIC1b (SEQ ID NO: 8), the claims clearly present a specific and well-established utility.

The Applicants respectfully submit that the claimed ASIC channels have a well-established specific and substantial utility, and the claimed channels can readily be used by those skilled in the art. The PTO must study the record to determine if there is a well-established utility for the claimed invention in making a utility determination. A well-established utility is recognized when the record discloses or suggests an activity for the protein or nucleic acid in question.

The Applicants respectfully submit that the Applicants' ASIC channels are clearly associated with a number of activities, and these activities can readily be used by those skilled in

the art. The Applicants show that ASIC is activated by extracellular acidification. It is well known in the art that sensitivity to acid is closely correlated to nociception and taste transduction. ASIC conducts the flux of ions through the membranes of cells, which results in the movement of action potential and cell signaling. Ionic channels are responsible for a number of specific cellular activities including the propagation of nerve impulses. For example, an article by S. Grillner. entitled *Bridging the Gap-From Ion Channels to Networks and Behavior*, Curr. Opin. Neurobiol. 1999. 9: 663-669 (copy of abstract enclosed), notes a number of neurodegenerative diseases that are known to be associated or caused by ion channelopathies.

The Applicants submit a copy of the OMIM report of amiloride-sensitive degenerine sodium channels for the Examiner's consideration. The Applicants respectfully submit that this report reviews the vital role amiloride-sensitive degenerine sodium channels play in physiological function, their association with molecular defects, and their use as a target for therapeutics. It is well known in the art that ASIC is a part of the superfamily of acid-sensing ion channels, which are proton-gated, amiloride-sensitive sodium channels. Furthermore, the Applicants respectfully submit that simply because MDEG is activated at a different pH, it does not follow that MDEG and ASIC channels are completely dissimilar. It simply means that within the family of amiloride-sensitive degenerine sodium channels there is some variation in physiological kinetics. In fact, page 17, line 26 to page 18, line 1 notes that the biophysical and pharmacological properties of the claimed ASIC channels are close to those that are described for the amiloride-sensitive proton-activated cationic channels.

The Applicants respectfully submit that the art has clearly recognized the role of amiloride-sensitive degenerine sodium channels in neurons and their correlation to disease states, such as Alzheimer's disease. This knowledge, coupled with the description of the Applicants'

ASIC channels, provides a precise target for the development of therapeutic treatments. This is especially true, in light of the large number of channel inhibitors and openers that are known in the art. The amiloride-sensitive degenerine sodium channel modulators provide significant therapeutic opportunities in physiological systems ranging from the neural to the immune system. The Applicants respectfully submit that at the time of the Applicants' invention, amiloride-sensitive degenerine sodium channels were known to be expressed throughout the brain. (See Darboux I, Biochem Biophys Res Commun. 1998 May 8;246(1):210-6, copy of abstract enclosed). With this background in mind, the Applicants set out to characterize additional members of this family.

The Applicants have thoroughly described a number of specific activities of the claimed ASIC channels. In particular, the Applicants' Specification discloses that: 1) ASIC electrophysiological currents are highly sensitive to extracellular pH (e.g. a change in pH alters ASIC's activity) ; 2) ASIC is expressed abundantly in brain and the small neurons of the dorsal root ganglion, the olfactory bulb, the cerebral cortex, the hippocampus, the habenula, the cerebellum, and the basolateral amygdaloid nucleus (e.g. it has an important role in brain activity); 3) ASIC is blocked by amiloride, benzamil and EIPA (e.g. it is sensitive to pharmacological products). In fact, since the Applicants' discovery of the claimed ASIC channels, and the elucidation of its expression and activity in the brain, Yermolaieva et al., 2004, PNAS, vol. 101, pg. 6752-6756, confirmed physiological role of ASIC channels in cerebral ischemia. (copy of abstract enclosed) Further, Wemmie et al., 2004 PNAS, vol. 101, pg. 3621-3626 and Wemmie et al., 2003, J. Neurosci., vol. 23, pg. 5496-5502 confirmed that ASIC is associated with fear and anxiety disorders (copy of abstract enclosed). Finally, Babini et al., 2002 JBC, vol. 277, pg. 41597-41603 describes the difference between splicing variants of the

ASIC channel. These differences illustrate that ASICb is more active at an acidic resting pH when compared to ASICa.

These activities allow one skilled in the art to use the Applicants' ASIC channels to:

1) target specific compounds to ASIC to modify ASIC's action potential in localized brain tissue;

2) use the activity patterns of ASIC to screen for therapeutic compounds, which inhibit ASIC activity in localized brain tissue culture;

3) use ASIC's expression pattern, to evaluate and provide treatment for individuals suffering from neurological disorders;

4) use ASIC for molecular diagnostics; and

5) use ASIC to evaluate nociception and taste transduction.

In view of the foregoing, the Applicants respectfully submit that the Specification describes a number of well-recognized activities and resulting uses for the Applicants' ASIC channels. Thus, utility has been shown.

The Applicants further respectfully submit that the Applicants' ASIC channels are directly analogous to DNA ligases. Therefore, the Applicants respectfully submit that examination of utility undertaken in Example 10 of the Revised Interim Utility Guidelines is analogous to the examination to be undertaken in this Application. It is well known in the art that amiloride-sensitive degenerine sodium channels conduct the flux of sodium through the membranes of living cells, and are expressed abundantly in the brain. As is well known in the art, mutations of the degenerins (deg-1, mec-4, mec-10) are the major known causes of hereditary neurodegeneration in the nematode Caenorhabditis elegans. (See Waldmann, R.; Champigny, G.; Voilley, N.; Lauritzen, I.; Lazdunski, M.: *The mammalian degenerin MDEG,*

an amiloride-sensitive cation channel activated by mutations causing neurodegeneration in Caenorhabditis elegans., J. Biol. Chem. 271: 10433-10436, 1996., copy enclosed) It is also known that amiloride-sensitive degenerine sodium channels are important in nociception and taste transduction. This family of channels are known to be responsible for the sensation of pain that accompanies tissue acidosis particularly during inflammation and ischemic conditions. (See Bevan, S., and Yeats, J. (1991) J. Physiol. (Lond.) 433, 145–161 Akaike, N., and Ueno, S. (1994) Prog. Neurobiol. 43, 73–83 Krishtal, O. A., and Pidoplichko, V. I. (1981) Neuroscience 6, 2599–2601). The Applicants respectfully submit that the physiological significance and physiological role of amiloride-sensitive degenerine sodium channels is clearly well-established.

Similarly, Example 10 describes a DNA ligase. The claimed DNA ligase in Example 10 has well-established utility because DNA ligases are known to be able to ligate DNA. The Applicants respectfully submit that DNA ligase is a class of enzyme involved in catalyzing the linkage of preformed deoxyribonucleotides in phosphodiester linkage during genetic processes and during repair of a single-stranded break in duplex DNA. The class includes both ATP and NAD. Exemplary DNA ligases include DNA ligase I to DNA ligase IV. Each of these different DNA ligases link DNA in particular physiological conditions, and through distinct molecular mechanisms. For example, DNA ligase III seals DNA strand breaks that arise during the process of meiotic recombination in germ cells and as a consequence of DNA damage in somatic cells, while DNA ligase IV joins single-strand breaks in a double-stranded polydeoxynucleotide in an ATP-dependent reaction. Furthermore, DNA ligase IV differs from DNA ligases I and III in its substrate specificity. Nevertheless, DNA ligases are still part of the same family of proteins.

In comparison, the Applicants disclose a member of the amiloride-sensitive degenerine sodium channel family. Moreover, the Applicants have gone a step further and disclosed a

amiloride-sensitive degenerine sodium channels having specific molecular activity. This specific activity allows one skilled in the art to identify potent therapeutics that modulate the activity of ASIC, and thus modulate action potentials of brain cells. These activities further allow for diagnostic evaluation of neurodegenerative disorders.

The Applicants respectfully submit that the newly identified ASIC plays a critical role in ionic transport in much the same way as DNA ligases inherently play a critical role in linking DNA strands. Consequently, the Applicants respectfully submit that ASIC channels, like DNA ligases, are recognized in the art as having a well-established, specific and substantial utility.

A study of Example 10 of the Utility Guidelines reveals that utility is met once one skilled in the art recognizes that the claimed enzyme is a DNA ligase (e.g. that it catalyses the linking of two molecules). Nothing in Example 10, however, demands that the disclosed DNA ligase must describe various disease states associated with the particular DNA ligase, the tissue expression of the DNA ligase, or its use to detect a disease state. All that is required in Example 10, is identification that the disclosed sequence was a DNA ligase. From there, one skilled in the art can readily recognize that the DNA ligase in question possessed a well-established utility. Essentially, one skilled in the art can readily appreciate that the DNA ligase in Example 10 had inherent utility by simply being a DNA ligase. Accordingly, the Applicants respectfully submit that the Specification does not need to demonstrate specific diseases associated with the claimed ASIC channel, its use to detect a disease state, or its tissue distribution. Nevertheless, the Applicants have gone far beyond the requirement and identified the tissue where ASIC is expressed and identified compounds that modulate ASIC activity.

The Applicants have shown that ASIC channel electrophysiological currents are sensitive to extracellular pH, and inhibited by amiloride, benzamil, and EIPA. The Applicants have also

described that ASIC transcript is abundantly expressed in brain and, in fact, identified specific regions of the brain where ASIC is expressed. In other words, the Applicants have identified particular compounds that can affect the flux of ions in the brain. It is respectfully submitted that such a discovery clearly possesses biological significance. Given this vast amount of knowledge, one skilled in the art can readily determine a number of potent pharmacological compounds that can be targeted to the ASIC channels in the brain.

Consequently, the Applicants respectfully submit that the Specification provides ample in-vitro data to demonstrate the specific activity of the claimed potassium channel. As discussed in the MPEP, in-vitro data is sufficient to establish the therapeutic utility of a compound, composition or process. See MPEP §2107.3. In this case, in-vitro studies have revealed the significant biological role of ASIC. As a result, the Applicants respectfully submit that the Specification establishes therapeutic utility for ASIC.

Pharmacological or therapeutic related inventions that provide "**any immediate benefit to the public**" satisfy 35 U.S.C. §101. Nelson v. Bowler, 206 USPQ 881, 83 (CCPA 1980) (Emphasis added). The Applicants have identified that ASIC likely has an important role in nociception and taste transduction, as described on pages 8-9 of the Specification. Clearly, the Applicants' discovery provided an immediate benefit to the public. For example, this invention allows the identification of potent therapeutics that can modulate the activity of the ASIC channel in the brain as well as provide insight into the in-vivo expression of ASIC. This information permits the diagnosis and treatment of neurodegenerative dysfunction that may arise as result of mutations from a ASIC gene. In view of the foregoing, the Applicants respectfully request the withdrawal of the rejection of Claims 1, 11, 12-13, 15, 17, 18-23, and 26-29 under 35 U.S.C. §101.

The Applicants respectfully submit that the Application is now in a condition for allowance, which is respectfully requested.

Respectfully submitted,

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